REMARKS

Present Status of the Application

Claims 19-21 and 23 remain pending. The Office Action dated August 11, 2009 again objected the specification for containing sequence disclosures as set for in 37 C.F.R. 1.821-1.825. Claims 19-21 and 23 were rejected under 35 U.S.C. 112, first paragraph for failing to comply with the enablement requirement.

Claim 19 has been amended for clarification purposes. It is believed that the amendments are supported by the original specification and drawings of this application and can overcome the objections. After entering the amendments and considering the following discussions, a notice of allowance is respectfully solicited.

Discussion for the objections

The specification was objected for failing to comply with the requirements of 37 C.F.R. 1.821-1.825 because pages 13, 17 and 36 of disclosure contain sequence disclosures requiring SEQ ID NOs..

The specification has been amended by assigning SEQ ID NOs. to the sequences recited in page 13, 1st paragraph to page 14, 1st paragraph, page 17 and page 36 of the specification of the present application, in the previous Responses.

Regarding the sequences recited in page 13 of the specification of the present application, nucleotide sequences comprising four or more than four nucleotides have been assigned with a

SEQ ID NO. respectively. According to the previous Office Action, nucleotide sequences comprising less than four nucleotides are not assigned with a SEQ ID NO..

Please find enclosed a new Sequence Listing in both computer readable form (CRF) and paper copy. Applicant confirms that the paper and electronic versions of the newly submitted Sequence Listing are identical and do not contain new matters. The new Sequence Listing incorporates sequences of SEQ ID NOs. 101 to 163 and additionally including sequences 97 to 100 which were assigned to sequences of pages 17 & 19 of the present application in response to the previous Office Action.

Withdrawal of these objections is earnestly requested.

Discussion of 112 rejections

Claims 19-21 and 23 were rejected under 35 U.S.C. 112, first paragraph for failing to comply with the enablement requirement. Especially, the Office Action considers that the specification enables a method of promoting regeneration and reconnection of damage neural pathways comprising the administration of an effective amount of SEQ ID NO:3, but not enabling such method comprising the administration of an effective amount of at least one oligonucleotide having a sequence at least 80% identical to a sub-sequence of SEQ ID NO:1 comprising 8 to 50 nucleobases.

Claim 19 has been amended to delete the term "termination codon".

Therefore claim 19 refers now to oligonucleotides that are directed to the region encompassing the translation initiation codon of the ORF of the gene encoding TGF-βRII, only. This is the same region the oligonucleotide with SEQ ID NO. 3 is directed to. Thus, the oligonucleotides claimed by amended claim 19 contain SEQ ID NO. 3 as a core sequence, or the oligonucleotides claimed by amended claim 19are very similar to SEQ ID NO. 3.

From Examples 6-8 of the specification of the present application, it has been proven that SEQ ID NO. 3 has activity in promoting successful regeneration and functional reconnection of damaged neural pathways. Because the oligonucleotides claimed by amended claim 19 contain SEQ ID NO. 3 and have a sequence very similar to SEQ ID NO. 3, the oligonucleotides claimed by amended claim 19 should show the same activity as SEQ ID NO. 3.

Therefore the oligonucleotides and their activity according to claim 19 are regarded as being very well supported by the specification of the present application and the enablement requirement is fulfilled.

The Examiner cites Ogorelkova et al. to show the unpredictability of the art of delivery of oligonucleotide therapeutics into target cells in vivo.

Ogorelkova et al. tested a set of adenovirus-delivered antisense RNA fragments and adenovirus-delivered shRNA molecules for their ability to target TGF-βRII. Ogorelkova et al. used a dicistronic reporter, consisting of the coding sequences for TGF-βRII and green fluorescent protein (GFP) to screen for optimal silencing agents targeting TGF-βRII. The activity of the antisense molecules was tested with cells transfected with the reporter, thus with exogenous TGF-βRII gene, and with cells without reporter, thus with endogenous TGF-βRII gene.

The results of Ogorelkova et al. show that the antisense RNAs were able to silence exogenous TGF-βRII but were unable to silence endogenous TGF-βRII. In contrast, the shRNAs were able to silence exogenous and endogenous TGF-βRII. Thus, from an activity on exogenous genes it can not be concluded whether there might be the same activity on endogenous genes.

However, Ogorelkova's results are of no relevance for the situation of the present application. The present application proves that its antisense oligonucleotides containing SEQ ID NO. 3 show a claimed therapeutic activity in **an in vivo animal model** (at least in Examples 7-8). The present application does not claim to be able to predict the activity of an antisense compound on the basis of a cell culture assay.

In addition Ogorelkova et al. present that antisense RNA or shRNA molecules with different but similar sequences show similar results for silencing TGF-βRII gene. For example, RNA molecules A, B and D included all the sequence of D and showed a similar extent of reduction of GFP fluorescence of the reporter construct (page 6, right column). This means that RNA molecules A, B and D showed a similar extent of silencing of exogenous TGF-βRII gene. Also shRNA molecules 1, 2, 3 and 4 contain similar sequences and all four scored positive for GFP reduction and were able to reduce expression of both transfected and endogenous TGF-βRII (page 12, left column, paragraph 2). Therefore in contrast to the understanding of the Office Action, Ogorelkova et al. rather supports our opinion that the oligonucleotides according to claim 19 show the same activity as SEQ ID NO. 3, because they contain SEQ ID NO. 3 or a sequence very similar to SEQ ID NO. 3.

Therefore the oligonucleotides and their activity according to claim 19 are very well supported by the specification of the present application and the enablement requirement is fulfilled.

Withdrawal and reconsideration of these 112 rejections are respectfully requested.

CONCLUSION

For at least the foregoing reasons, it is believed that the pending claims of the present application patently defines over the prior art and are in proper condition for allowance. If the Examiner believes that a telephone conference would expedite the examination of the above-identified patent application, the Examiner is invited to call the undersigned.

Respectfully submitted,
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Date: November 9, 2009

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